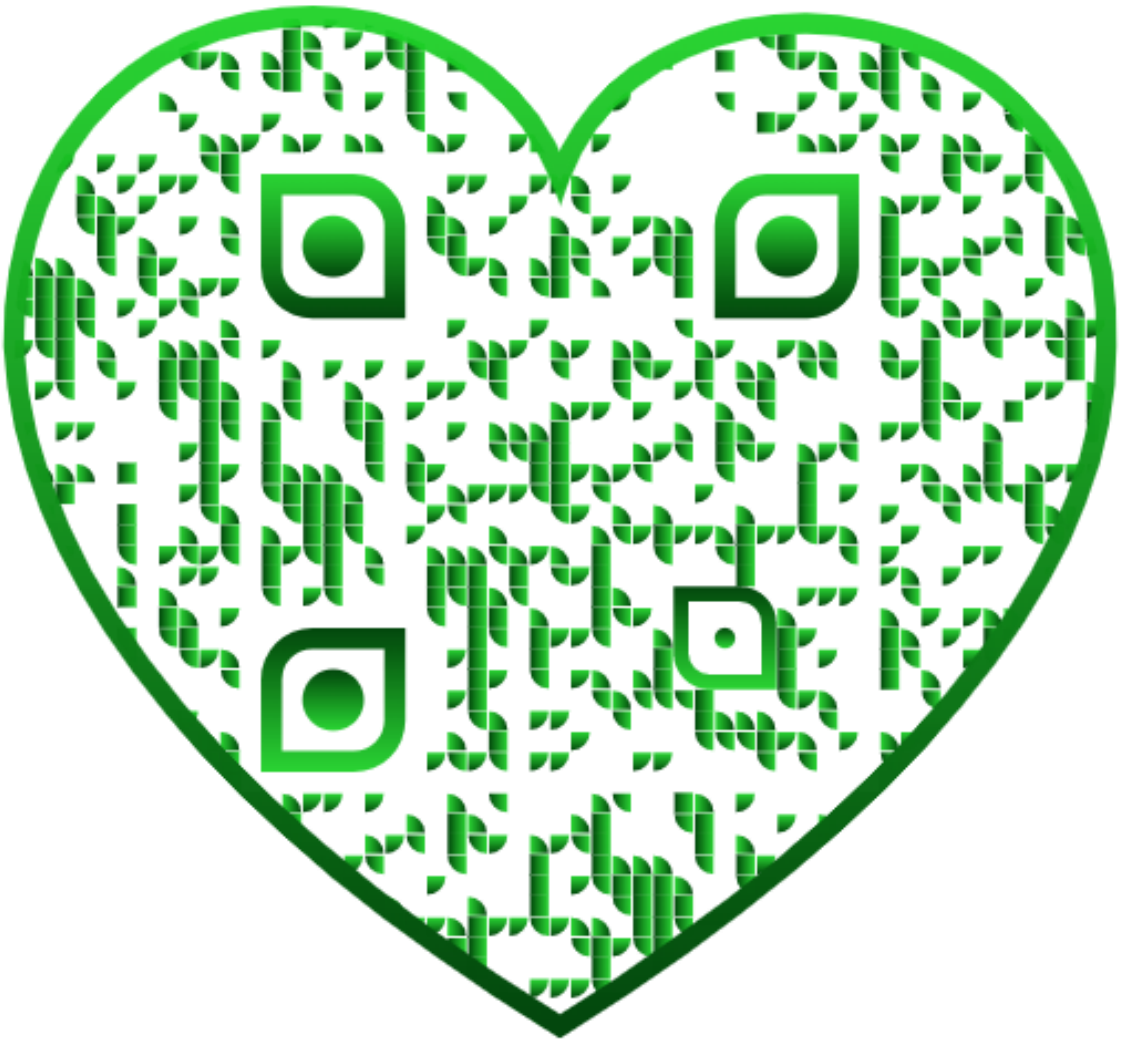
3. Micromeritics

- **Particle size and size distribution**
- **Particle shape and surface area**
- **Derived properties of powders**



Introduction

Micromeritics

- Micromeritics is the science of small particles.
- It deals with **fundamental** and **derived** properties of individual and collection of particles.
  - Particle size and size distribution,
  - Particle shape,
  - Angle of repose, porosity, true volume, bulk volume, apparent density, and bulkiness.

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- Micromeritics studies of a number of characteristics, including:
  - Particle size and size distribution,
  - Particle shape,
  - Angle of repose, porosity, true volume, bulk volume, apparent density, and bulkiness.

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- Solids are unique because their physical form can have an influence on the way the material will behave.
- Solid particles are made up of molecules that are held in close proximity to each other by intermolecular forces.
- The strength of interaction between two molecules is due to the individual atoms within the molecular structure.

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- Micromertics has become an important area of study because it influences a large number of parameters,
  - Research and development
  - Manufacturing of dosage forms such as:
    - Suspension to be reconstituted
    - Tablet
    - Capsule

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- It is important to study particles because most drug dosage forms are solids,
  - Solids are not static systems,
  - The physical state of particles can be altered by physical manipulation, and
  - Particle characteristics can alter therapeutic effectiveness.
    - Particle size, and hence SA of a particle can be related in a significant way to the physical, chemical, and pharmacologic properties of a drug.

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- Study of particle size and size distribution has many application in pharmacy
  - Physical properties of powder are dependent on particle size and size distribution
  - Flow properties of the powder (Spherical/Asymmetrical)
  - Release & dissolution
  - Absorption & drug action
  - Physical stability
  - Dose uniformity

- Fundamental properties of collection of particles
  - Particle size and size distribution
  - Particle shape and surface area
  - Particle number and weight
  - Particle volume

- Derived properties of collection of particles
  - Porosity
  - Packing arrangement
  - Density
  - Bulkiness
  - Flow properties
  - Compaction

Particle Size and Size distribution

Particle size

- Particle size determinations are complicated by the fact that particles are not uniform in shape.
- Particle shape plays an important role in particle size determination
  - Particles possess different shapes
  - The size of a spherical particle can be easily expressed in terms of its **diameter**

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- So, for a perfect sphere;
  - Surface area, SA = πd^2
  - Volume, V = $\frac{\pi d^3}{6}$
- Non-spherical particles also has a definite SA and volume, but being asymmetric its apparent length varies with its orientation.
  - Hence, it is not possible to express its size in terms of its diameter.

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- Various equivalent diameters have been developed to relate the size of such particles to that of a sphere:
  - **Surface diameter** (d_s) the diameter of a sphere having the same SA as that of the asymmetric particles in question.
  - **Volume diameter** (d_v) the diameter of a sphere having the same volume as that of the asymmetric particles in question.

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- **Projected diameter** (d_p) the diameter of a sphere having the same observed area as that of the asymmetric particles in question.

- **Stock diameter** (d_{st}) the diameter of a sphere with the same density (Which undergoes sedimentation at the same rate) as the asymmetric particles in question.

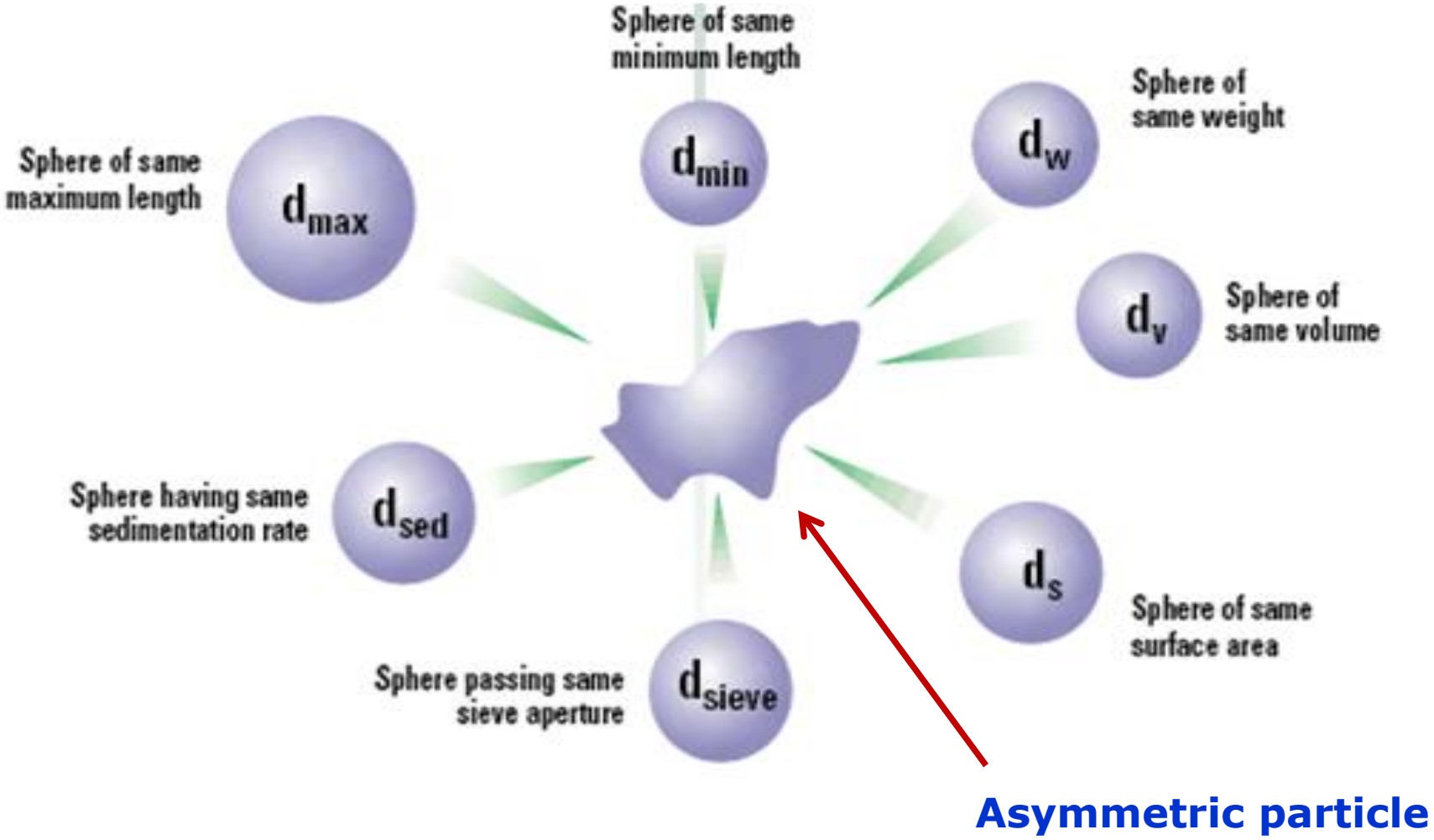

Fig. Different Equivalent Spheres

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- Particle size influences the production of formulated medicines as solid dosage forms.
- Powders with different particle sizes have different flow and packing properties.
  - Which alter the volumes of powder during encapsulation or tableting.
  - Particle sizes of powders may be defined during formulation to avoid such problems.

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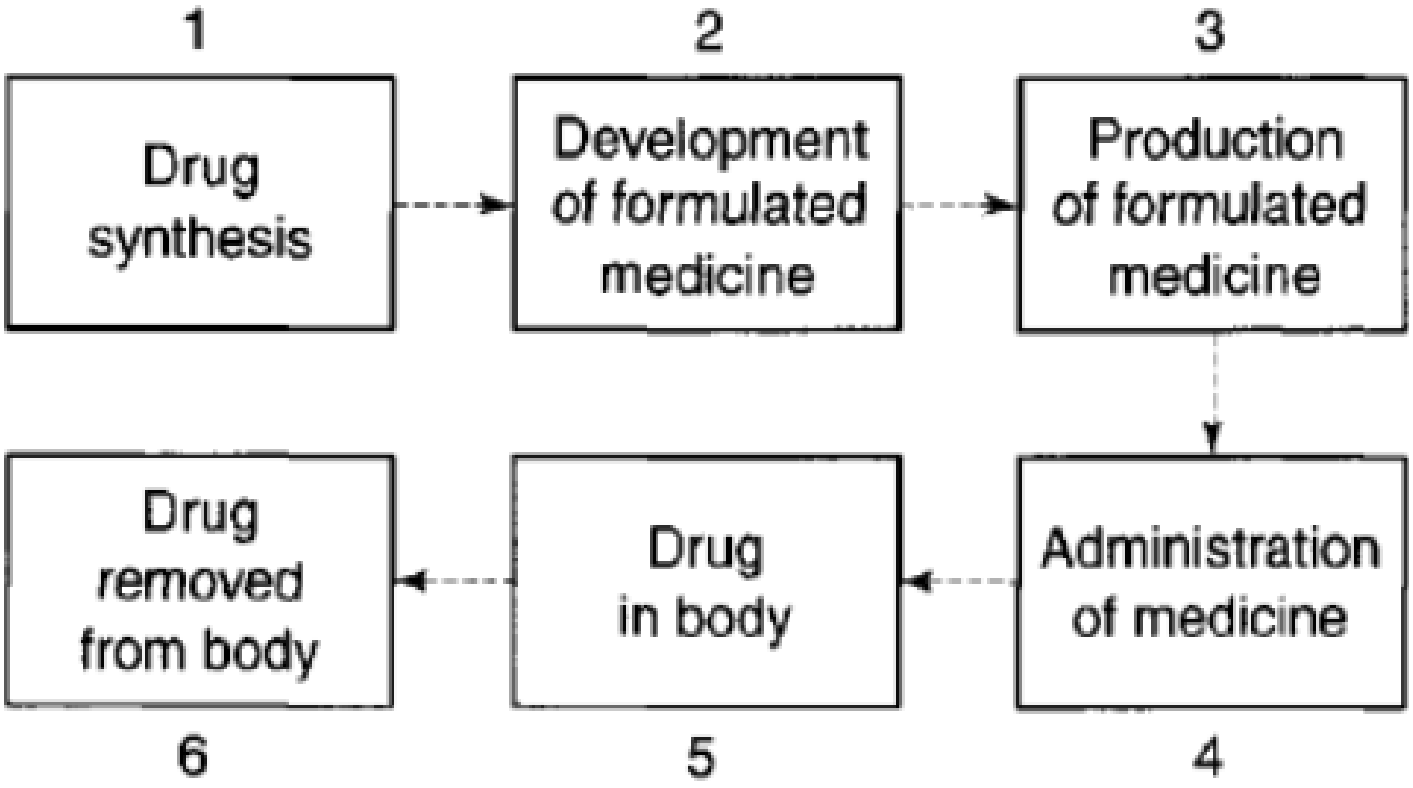
- Following administration of the medicine, the dosage form should release the drug into solution at the optimum rate.
- This depends on several factors, one of which will be the particle size of drug.
- Noyes and Whitney first showed that the rate of solution of a solid was related to the law of diffusion. (Refer to the equation and description)


1
Drug synthesis
2
Development of formulated medicine
3
Production of formulated medicine
4
Administration of medicine
5
Drug in body
6
Drug removed from body

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- In a polydisperse sample, two properties are important:
  - The shape and SA of the individual particles
  - The size range and number/weight of particles present (the total surface area) (called particle size distribution)

Average particle size

- The particle size of a powder is analyzed microscopically and the number of particles in each size range is determined

- From the data (table below) the average particle size of the powder may be calculated as:

$$\text{Particle size} = \frac{\sum nd}{\sum n}$$

$$= 2.16\ \mu m$$

Size range (μm)	Mean size range (in μm) (d)	No particle in each size range (n)	nd
0.5-1.0	0.75	4	3
1.0-1.5	1.25	18	22.5
1.5-2.0	1.75	39	68.25
2.0-2.5	2.25	73	164.25
2.5-3.0	2.75	24	66
3.0-3.5	3.25	14	45.5
3.5-4.0	3.75	2	7.5
		$\Sigma n=174$	$\Sigma nd=377$

Particle size distribution

- The particle size distribution in a powder may be quantified by
  - Determining the **number** of particles present in each size range
  - Determining the **weight** of particles present in each size range

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- When this number/weight of particles lying within a certain size range is plotted against size range or mean particle size - Frequency distribution curve is obtained;
  - Number frequency distribution curve - number of particles vs mean particle size
  - Weight frequency distribution curve - weight of particles vs mean particle size

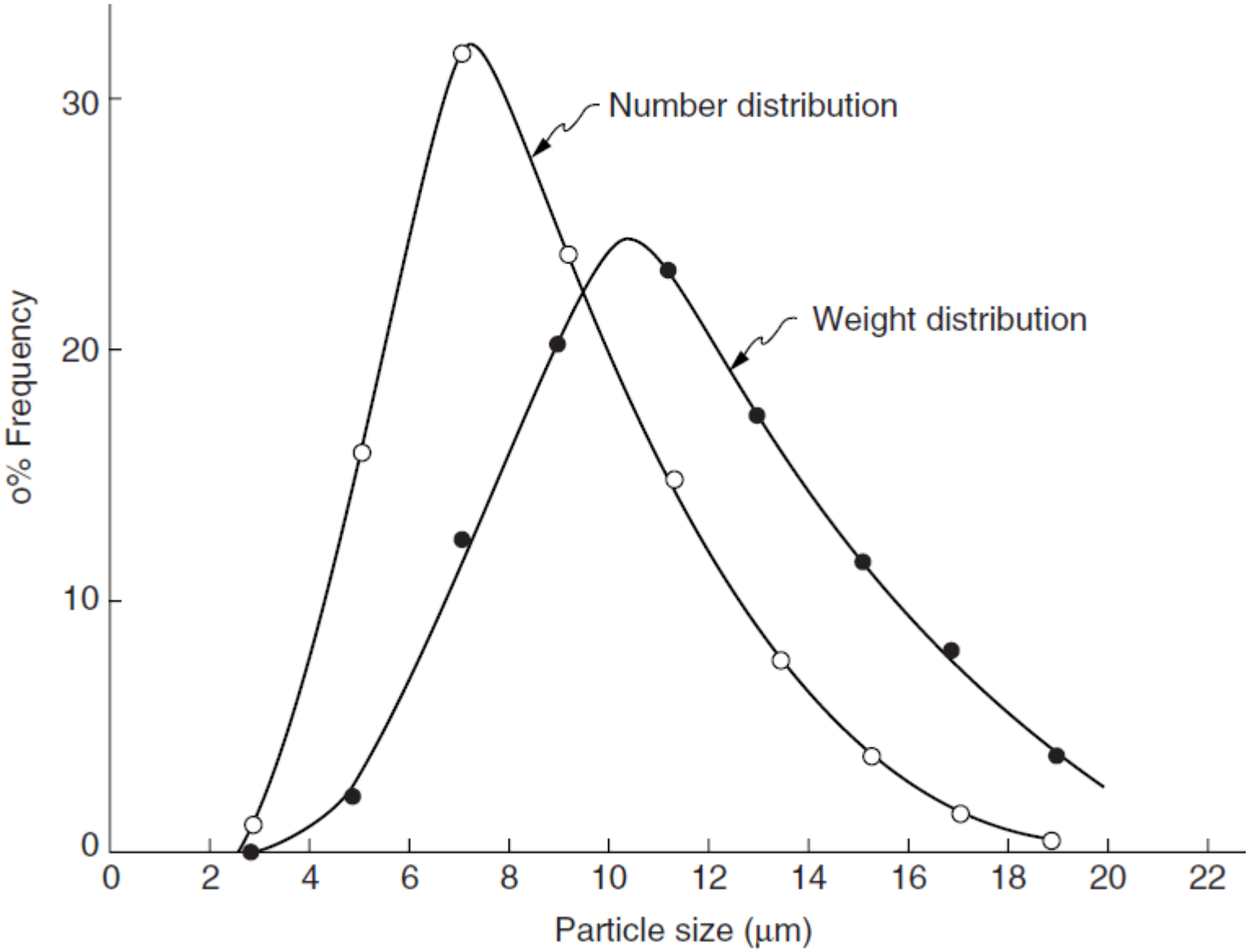

Fig. A frequency distribution plot.

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- Two sample of powder may have the same average diameter but may not have the same frequency distribution.
  - So, expression of the size in terms of average diameter may not give a clear expression of the particle size distribution
- From frequency distribution curve, we obtain:
  - Particle size distribution
  - The particle size which occur most frequently

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- Normal distribution is not common in pharmaceutical powders.
- More commonly asymmetric or skewed distribution is obtained.
  - Positively skewed - A frequency curve with an elongated tail towards higher size ranges, or
  - Negatively skewed - A frequency curve with an elongated tail towards smaller size ranges.

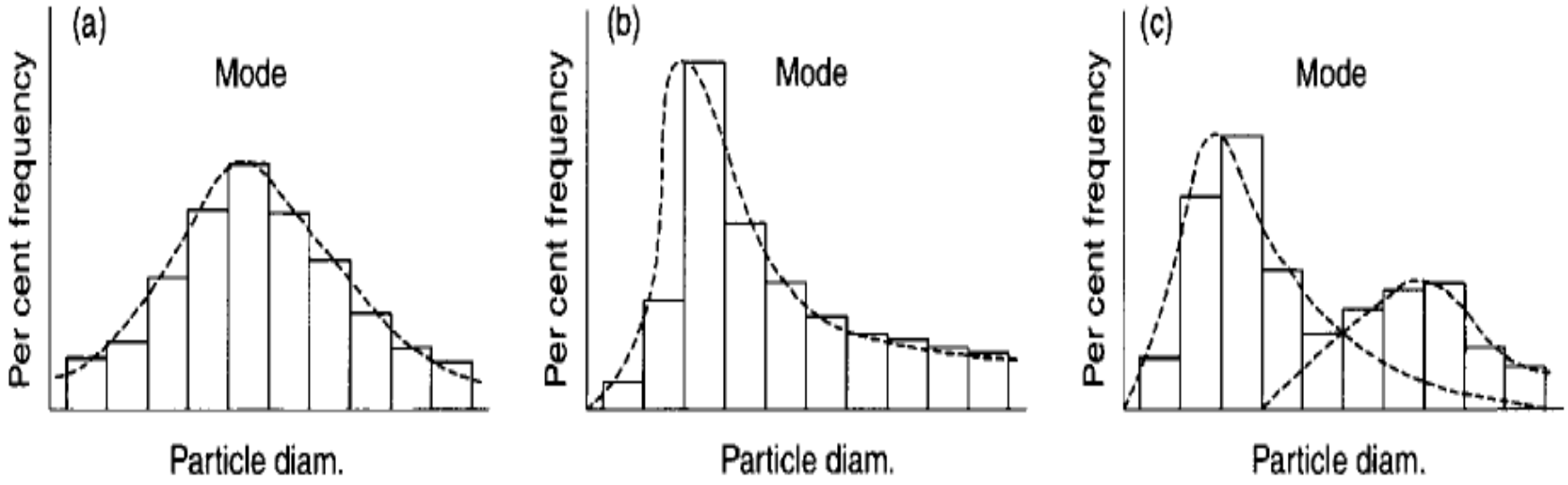

Fig. Frequency distribution curves corresponding to (a) a normal distribution, (b) a positively skewed distribution and (c) a bimodal distribution.

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- Such a curve can be converted to a normal bell shaped curve by plotting frequency vs the logarithm of the particle size diameter

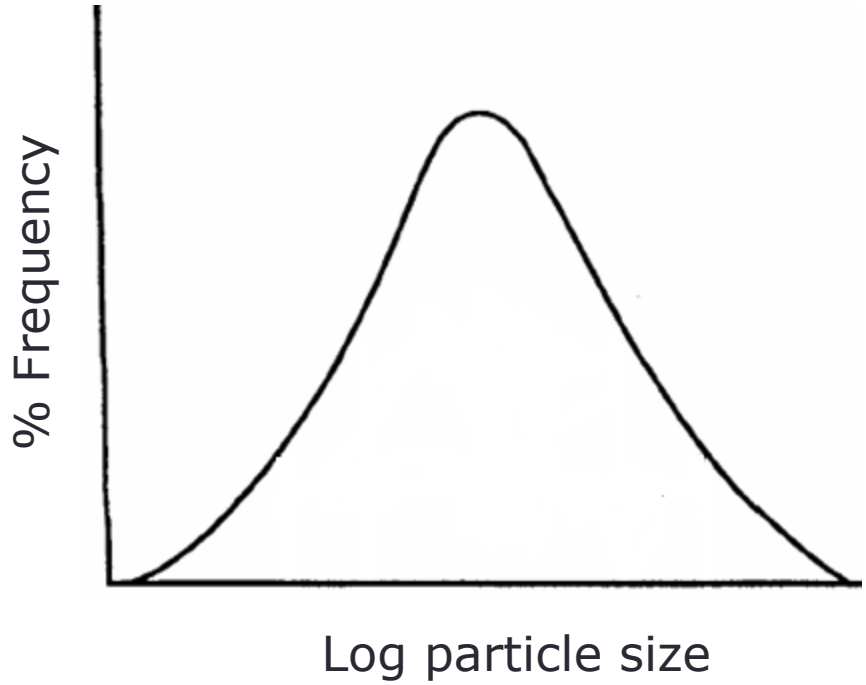

Fig. Log normal distribution curve obtained for a polydisperse powder

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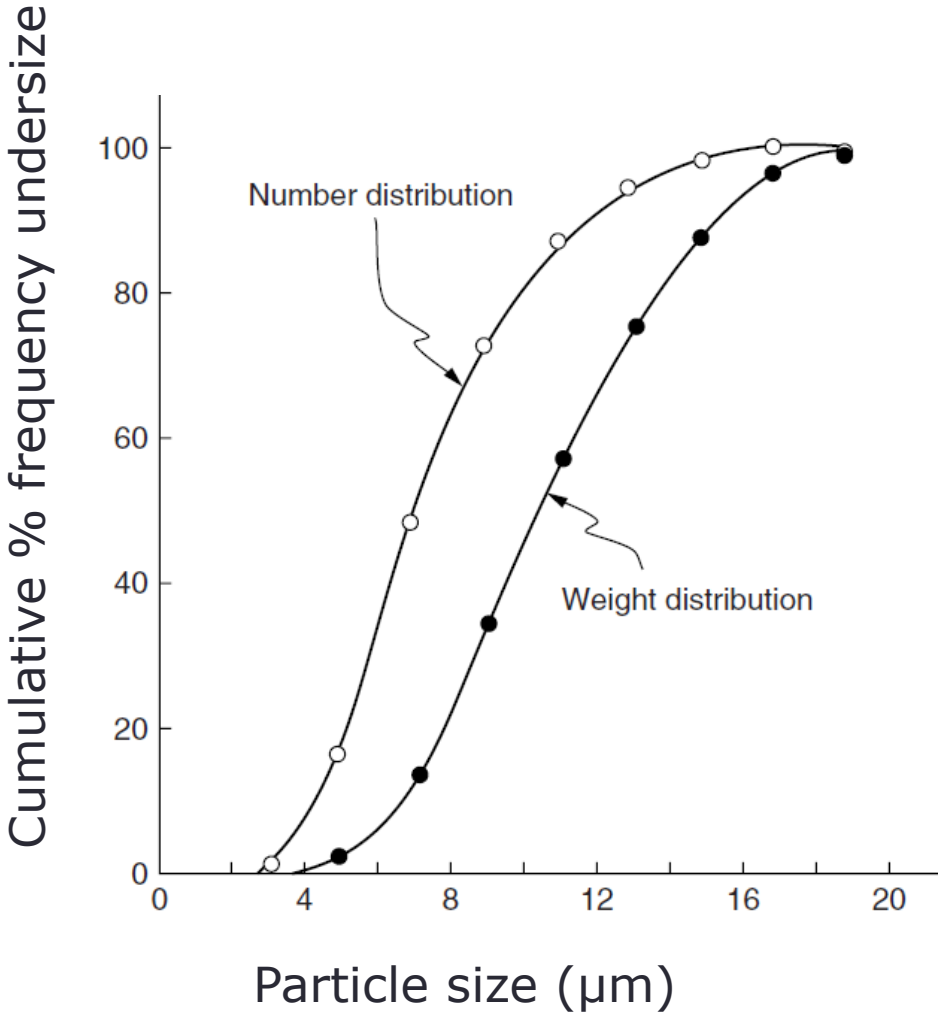
- A cumulative percent frequency distribution can also be obtained by sequentially adding the percent frequency values.
  - Cumulative percent frequency **undersize** - If the addition sequence begins with the coarsest particles.
  - Cumulative percent frequency **oversize** - If the addition sequence begins with the finest particles.

Cumulative frequency distribution data

Equivalent particle diameter (μm)	Per cent frequency	Cumulative per cent frequency Undersize	Oversize
20	4.5	4.5	100
40	9.1	13.6	95.5
60	18.2	31.8	86.4
80	36.4	68.2	68.2
100	18.2	86.4	31.8
120	9.1	95.5	13.6
140	4.5	100	4.5

- Cumulative percent frequency distribution gives **sigmoid curve** with the mode being the particle size of the greatest slope.



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- When the log of the particle size is plotted against the cumulative percent frequency on probability scale a linear relationship is obtained.
  - This is known as the log probability plot.
  - Geometric mean diameter - It is the log of the particle size equivalent to 50% on the probability scale, i.e., the 50% size.

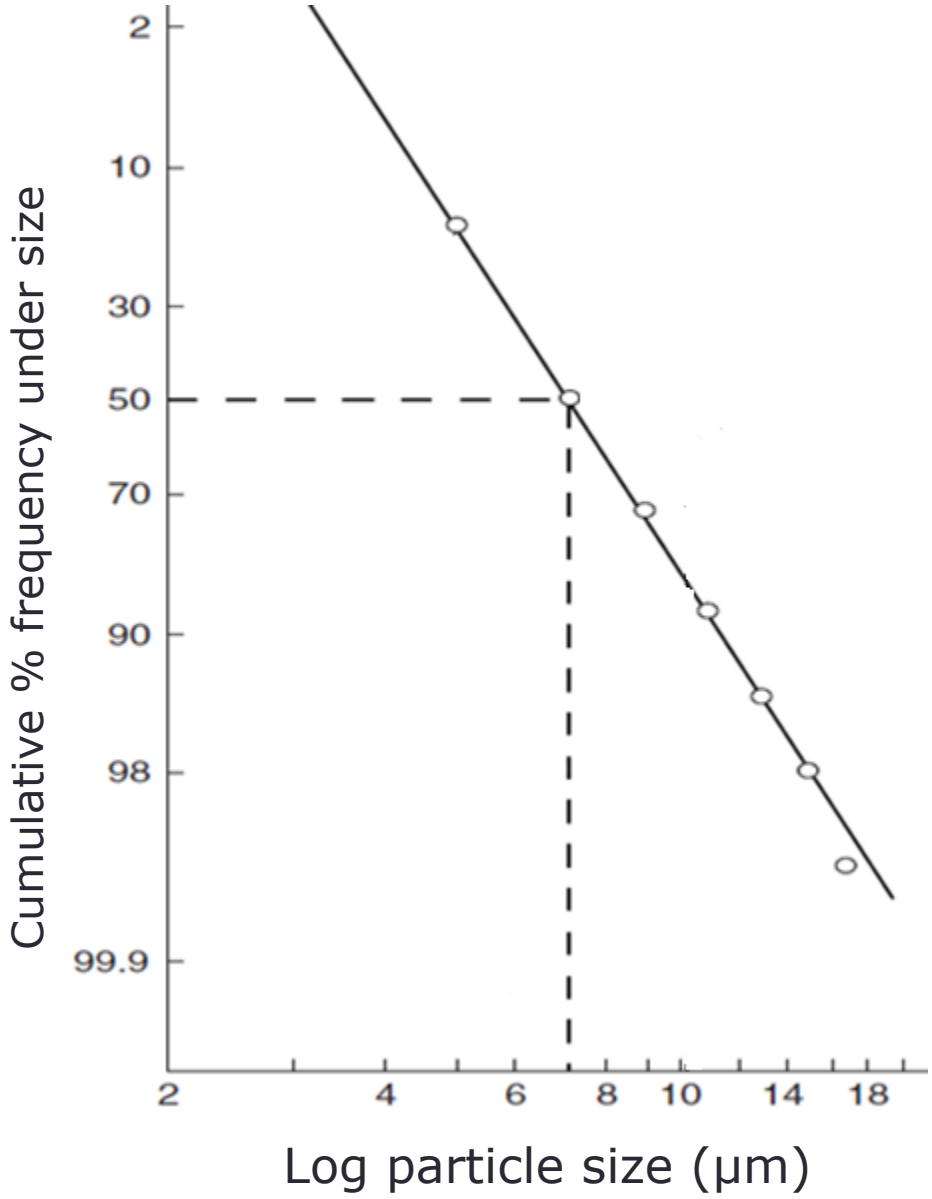

Fig. Log probability plot

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Types of Diameters

- Particle size (diameter) can be described by different expression

1. A mean particle diameter

    - The sum of all individual diameter divided by the total number of particles .

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2. Median diameter

- A diameter for which 50% of the particles are less the stated size.

3. Mode diameter

- Represent the particle size occurring most frequently

4. Mean volume surface diameter

- Used to express powder particle size in terms of surface area per unit volume.

Determination of particle size and size distribution

- Particle-size analysis methods can be divided into different categories based on several different criteria:
  - Size range of analysis
  - Wet or dry methods
  - Manual or automatic methods
  - Speed of analysis

- Different techniques are used for particle-size analysis:

    A. Microscopic technique

    B. Sieving technique

    C. Sedimentation technique

    D. Coulter counter technique

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A. Microscopy

- The microscope eyepiece is fitted with a **micrometer** by which the size of the particles may be estimated.

- The effective size range for analyzing particles is about 0.25 to 100 μm.

- Procedure:
  - A diluted suspension of the particles is prepared in a liquid in which it is insoluble.
  - A drop of suspension is placed on the slide.
  - The eyepiece of the microscope is fitted with micrometer
  - The particles observed are counted
    - For ease, the field can be **projected** or **photographed.**

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- Average diameter of a particulate system is obtained by measuring the particles at random along a given fixed line.
- At least 300 - 500 particles must be counted in order to obtain a good size distribution analysis of data.

- Advantages
  - Providing a direct visual representation of the particles.
  - Requires an extremely small amount of sample.
  - Needs no calibration by other methods.
  - The equipment is relatively inexpensive to acquire and maintain.
  - It can provide details about shape, crystal habit, and homogeneity within the sample in addition to size.

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- Disadvantage
  - The measured diameter of the particles represents two dimensions only.
  - Slow and tedious process.

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B. Sieving

- Uses nests of standard sieves stacked one over the other.
- Involves mechanical shaker.
- The particles on each sieve sizes are collected and weighed.
- Useful for coarse particles (>50 μm).

Table Openings of Standard Sieves, U.S. Series

Assigned number	Sieve opening
2	9.5 mm
3.5	5.6 mm
4	4.75 mm
8	2.36 mm
10	2.00 mm
14	1.40 mm
16	1.18 mm
18	1.00 mm
20	850 μm
25	710 μm
30	600 μm
35	500 μm
40	425 μm
45	355 μm
50	300 μm
60	250 μm
70	212 μm
80	180 μm
100	150 μm
120	125 μm
200	75 μm
230	63 μm
270	53 μm
325	45 μm
400	38 μm

- Procedure
  - A nest of sieves with the coarsest on top is placed on the shaker,
  - Powder sample of **known weight** is placed on the top of the sieve & shaken for a **defined time**.
  - The powder is classified as having passed through one sieve and being retained on the adjacent finer sieve.
  - Mass, Percentage or Cumulative percentage of sample retained on each sieve collected is determined.

- Limitations
  - Aggregation - due to electrostatic charge or moisture actual size is not determined
  - Attrition – will result in size reduction
  - Sieve loading and duration of mechanical shaking can influence the results

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C. Sedimentation

- The particle size in sub-sieve range can be obtained by gravity sedimentation as expressed in Stokes's law (0.8 to 300μm).

- Andreason pipette is used for particle size distribution determination.

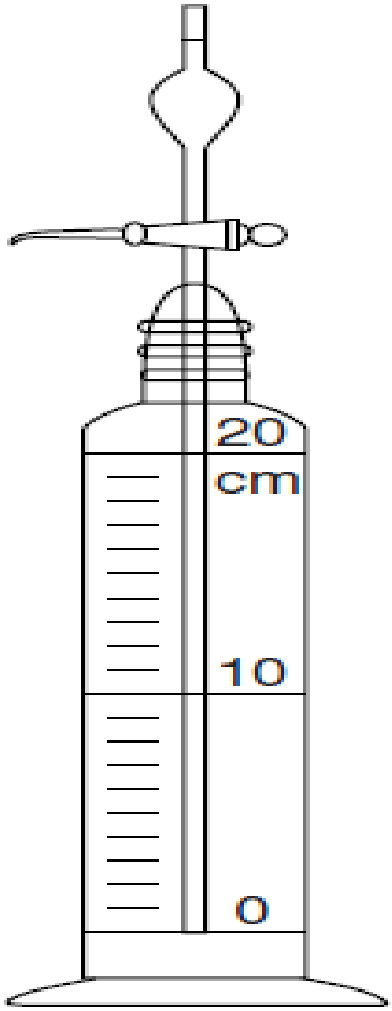

Fig. Andreason pipette

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- Procedure
  - 1 or 2% suspension of the powder is placed in the vessel up to 550 ml mark.
  - Shake for uniform distribution of the particles within the medium
  - Left undisturbed in constant temperature bath
  - 10 ml sample is drawn at various time interval
  - The samples are evaporated and weighed

- The particle diameter corresponding to the various time period is calculated using the Stocks equation

$$V = \frac{h}{t} = \frac{d_{st}^2(\rho_s - \rho_o)g}{18\eta_o}$$

- V is the rate of settling
- h is the distance of fall in time
- d_{st} is the mean diameter of the particles based on the velocity of sedimentation
- ρ_s is the density of the particles
- ρ_o is the density of dispersion medium
- η_o is the viscosity of the medium
- g acceleration due to gravity

- For Stokes law to apply,
  - Particles be spherical falling freely at a constant rate
  - Particles must not be aggregated
    - As clumps would fall more rapidly than individual particles
    - A proper deflocculating agent may be used

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- For Stokes law to apply, a further requirement is that the flow of dispersion medium around the particle as it sediments is **laminar** or stream line.
  - Whether the flow is turbulent or laminar is indicated by the dimensionless **Reynolds number**, R, which is defined by:

$$R = \frac{V d \rho_o}{\eta_o}$$

  - Stokes law cannot be used if R is greater than 0.2 because turbulence appears at this value.

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- The limiting particle size under a given set of conditions can be calculated as:

$$V = \frac{R\eta_o}{d\rho_o}$$

$$d^3 = \frac{18R\eta_o^2}{(\rho_s - \rho_o)\rho_o g}$$

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- Advantage
  - The apparatus is **inexpensive** and the technique is **simple**
  - The results obtained are **precise** provided the technique is adequately standardized
- Disadvantages
  - Method is **laborious** since separate analysis are required for each experimental point on the distribution curve
  - **Very small particles** cannot be determined accurately since their settling is unduly prolonged

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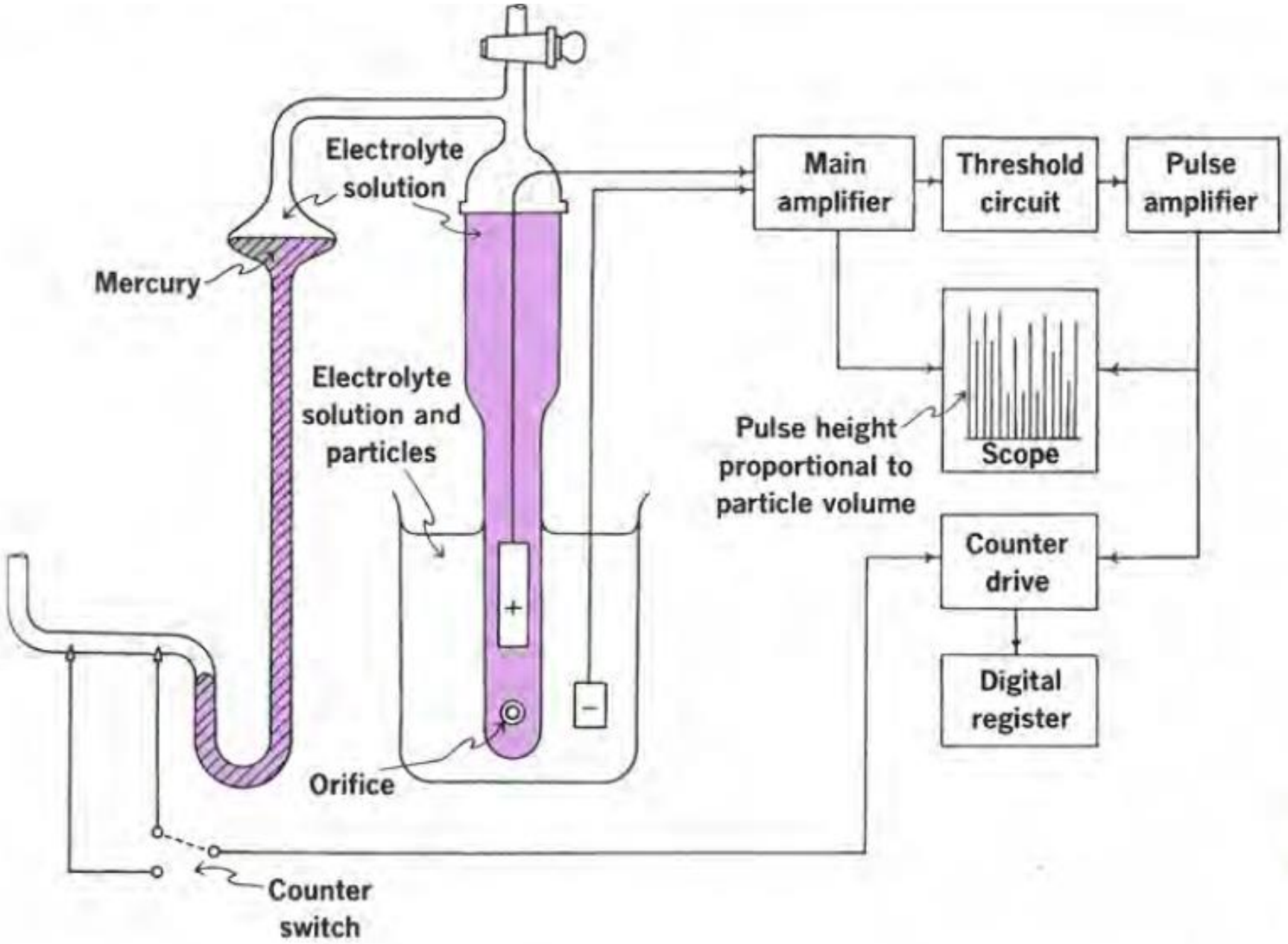
D. Coulter Counter Method

- **Principle**: when a particle suspended in a conducting liquid passes through a small orifice (opening), on either side of which are electrodes, a change in electric resistance occurs.

- Procedure
  - Powder samples are dispersed in the electrolyte to form a very dilute suspension.
  - A known volume of the suspension is pumped through the orifice so that only one particle passes at a time through the orifice
  - A constant voltage is applied across the electrodes so as to produce a current.
  - As the particle travels through the orifice, it displaces its own volume of electrolyte and this results in an increased resistance b/n the two electrodes.


Electrolyte solution
Mercury
Electrolyte solution and particles
Orifice
Counter switch
Main amplifier
Threshold circuit
Pulse amplifier
Scope
Pulse height proportional to particle volume
Counter drive
Digital register
+
−

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Derived Properties of Powders

a) Porosity of Powder

- Most pharmaceutical solids are porous, i.e., they have internal pores or capillary (Bulk volume > true volume)

- When a powder, is placed in a graduated cylinder: the total volume occupied is known as the **bulk volume** (V_b)

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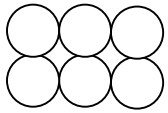
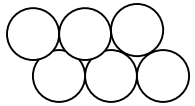
- Bulk volume (V_b) = True Volume (V_t) + Volume of spaces b/n particles (V).
- The volume of the spaces (void volume), $V = V_b - V_t$
- The porosity (ε) of powder is determined as the ratio of void volume to bulk volume.

$$\boldsymbol{Porosity\ (\varepsilon) = \frac{V_b - V_t}{V_b} = 1 - \frac{V_t}{V_b}}$$

- Packing arrangement in powder beds
  - Two types of packing are possible
    - **Cubic packing** - most open/loosest packing (ε = 48 %)



    - **Rhombohedral packing** - closest packing (ε = 26 %)



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- Pharmaceutical powders have porosity range from 30 and 50%.
- When the particles of varying sizes are present, porosity lower than the theoretical minimum of 26% is also possible (Why?)
- If the powder contains floccules or aggregates, the porosity may go beyond the theoretical maximum of 48% (Why?)
- Highly compressed crystalline materials, $\varepsilon < 1\%$

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b) Densities of particles

- Density is defined as weight per unit volume (W/V).
- Types of densities:

i. True density

- The true density, or absolute density, of a sample excludes the volume of the pores and voids within the sample.
- Determined by Liquid or Gas displacement method.

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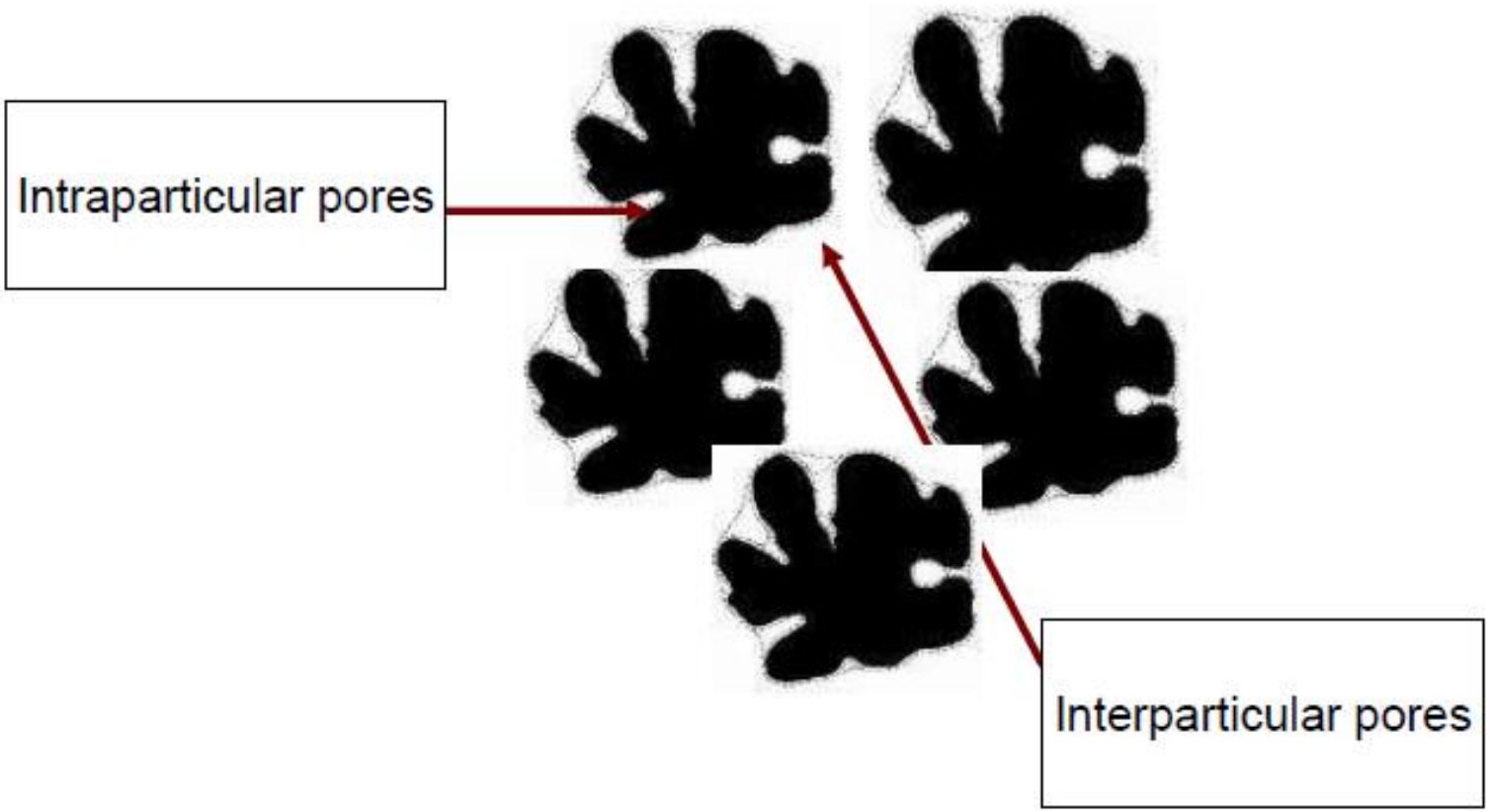
ii. Granule density

- Mass of the granular powder and the volume occupied by the granular material together with its **intra particle** space
- Determined by Liquid displacement method (Mercury)
- Mercury is used because it fills the void spaces but fails to penetrate into the internal pores of the particles.


Intraparticular pores
Interparticular pores

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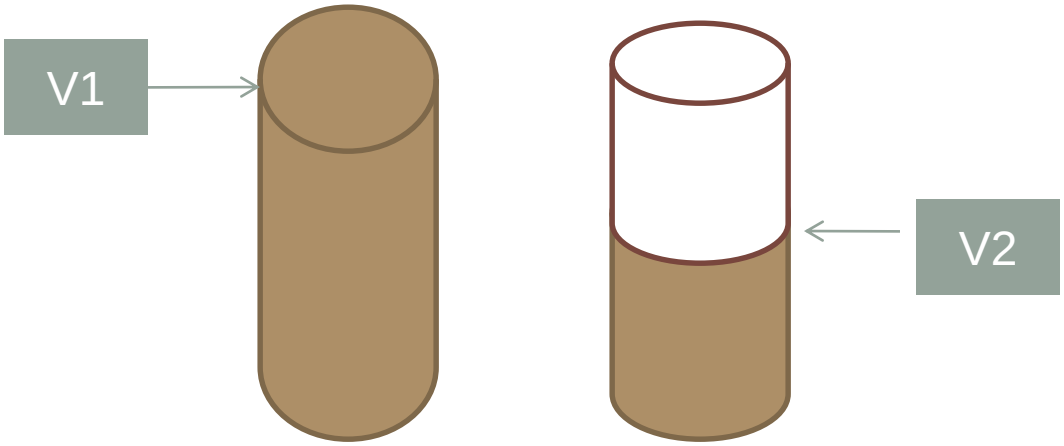
iii. Bulk density

- It is the ratio of the mass of the powder and its bulk volume (untapped powder) (V_1 below)
- Includes the volume of all of the pores within the sample.

iv. Tapped density

- It is the ratio of mass of powder to tapped volume (V_2 below)



$$\rho_b = \frac{M}{V_1} \qquad \rho_T = \frac{M}{V_2}$$

Fig. Tap densitometer

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c) Bulkiness (Specific bulk volume)

- The reciprocal of **bulk density**
- (Bulkiness usually increases with a decrease in particle size.) ??
- However, in a mixture of particles with different sizes, the bulkiness may get reduced. (Why?)
- Bulkiness is important while choosing a suitable container for packaging or during filling of powders into capsules.

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d) Flow properties of Powders

- Powders may be free-flowing or cohesive ("sticky").
- Die filling during tableting and capsule filling directly depend on the flow properties of the powder.
- Many common manufacturing problems are attributed to powder flow.

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- Flow properties of powders depends on:

1) Cohesiveness or stickiness between particles

    - Cohesiveness of particles has been found to depend upon a number of factors:

        - Particle size and shape
        - Density or porosity of the powders
        - The presence of adsorbed materials on the powder surface

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2) Adhesion between the particles and the container wall.

3) Friction between particles due to surface roughness.

4) Physical interlocking of particles specially if these are of irregular shape

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- Assessment of flow properties of powders

i. **Carr's compressibility index**

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Poured or bulk density}}{\text{Tapped density}} \times 100$$

Flow description	% compressibility
Excellent flow	5 – 15
Good	16 – 18
Fair	19 – 21
Poor	22 – 35
Very poor	36 – 40
Extremely poor	> 40

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ii. Hausner ratio:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured or bulk density}}$$

- Value less than 1.25 indicates good flow
- Value greater than 1.5 indicates poor flow
  - Between 1.25 and 1.5, added **glidant** normally improves flow.
  - > 1.5 added glidant doesn't improve flow.

iii. Angle of Repose (θ)

- The sample is poured onto a horizontal surface and the angle of the resulting pyramid is measured.

- The user normally selects the funnel orifice through which the powder flows slowly and reasonably constantly.

$$\tan\theta = \frac{h}{r}$$

- Angle of repose is a function of the surface roughness.
  - The rougher and more irregular the surface of particles, the more the angle of repose
- As the particles become less and less spherical, the angle of repose increases while the bulk density and flowability decreases.

Angle of repose (θ)	Flow properties
<25^o	Excellent
25 – 30^o	Good
40 – 50^o	Satisfactory
30 – 40^o	Poor
>50^o	Very poor

- Factors affecting the flow properties of powders

a) Alteration of Particle's size & Distribution

- There is certain particle size at which powder's flow ability is optimum.
- Coarse particles are more preferred than fine ones as they are less cohesive.
- The size distribution can also be altered to improve flowability by removing a proportion of the fine particle fraction.

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b) Alteration of Particle Shape & texture

- Generally, more spherical particles have better flow properties.
  - Spherical particles are obtained by spray drying, or by temperature cycling crystallization.
- Particles with very rough surfaces will be more cohesive and have a greater tendency to interlock than smooth surfaced particles

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c) Surface Forces and Moisture content

- Reduction of electrostatic charges can improve powder flowability.
- Moisture content of particle greatly affects powder's flowability.
  - Adsorbed surface moisture films tend to increase bulk density and reduce porosity.
  - Drying the particles will reduce the cohesiveness and improve the flow.

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d) Formulation additives (Flow activators)

- Flow activators are commonly referred as glidants.
- Flow activators improve the flowability of powders by reducing adhesion and cohesion.

  E.g. Talc, Maize starch and Magnesium stearate

4. Powders and Granules

- Solid oral dosage forms
  - Powder
  - Granules
  - Tablets
  - Capsules

Powders

- The term "powder" may be used to describe
  - The physical form of a material i.e. a dry substance composed of finely divided particles.
  - A type of pharmaceutical preparation - a medicated powder intended for internal (i.e., oral powder) or external (i.e., topical powder) use.

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- Powders may be dispensed to a patient
  - **Multiples dose** (bulk form such as powders measured by the spoonful to make a douche solution)
  - **Single dosage units**
- Powders represent one of the oldest dosage forms.
- However, with the increased use of highly potent compounds, they have been largely replaced by capsules and tablets.

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- In certain situation, powders still possess advantages
  - Powders disperse & dissolve more readily than compacted dosage forms.
  - Children and adults who have trouble swallowing tablets or capsules may find powders more acceptable.

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Formulation of powder dosage forms

- Size reduction and mixing are very important steps in the formulation of powders.
  - On a small scale, the size reduction is achieved by grinding with a mortar and pestle or with ointment tile and spatula
  - On a large scale, various types of mills and pulverizers may be used

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- **Trituration** or **comminution** is grinding a drug in a mortar to reduce its particle size.

- **Levigation** is commonly used in small-scale preparation of ointments and suspensions to reduce the particle size and grittiness of the added powders.

- **Pulverization by Intervention** - When it is difficult to powder a material in a mortar because it is soft or gummy, we add a second material which helps in the powdering and which is latter removed.

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- Effective mixing depends on:
  - Nature of the ingredients
  - Amount of powder
  - Equipment
- Powders may be mixed/blended by spatulation, trituration, sifting, and tumbling.

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- **Spatulation**
  - It is blending small amounts of powders by movement of a spatula through them on a sheet of paper or an ointment tile.
  - Not suitable for large quantities of powders or for powders containing potent substances
  - Good for mixing solid substances that form eutectic mixtures

...

- **Trituration**
  - May be employed both to comminute and to mix powders.
  - If simple admixture is desired without the special need for comminution, the glass mortar is usually preferred
  - When a small amount of a potent substance is to be mixed with a large amount of diluent, the **geometric** dilution method is used

- **Sifting**
  - Powders may also be mixed by passing them through sifters
  - Sifting results in a light, fluffy product.
  - It is not acceptable for the incorporation of potent drugs into a diluent powder.

- **Tumbling**
  - This is tumbling the powder in a rotating chamber
  - Special small-scale and large-scale motorized powder blenders mix powders by tumbling them
  - Mixing by this process is thorough but time consuming

Fig. Industrial-size solid-state processor (twin shell blender)

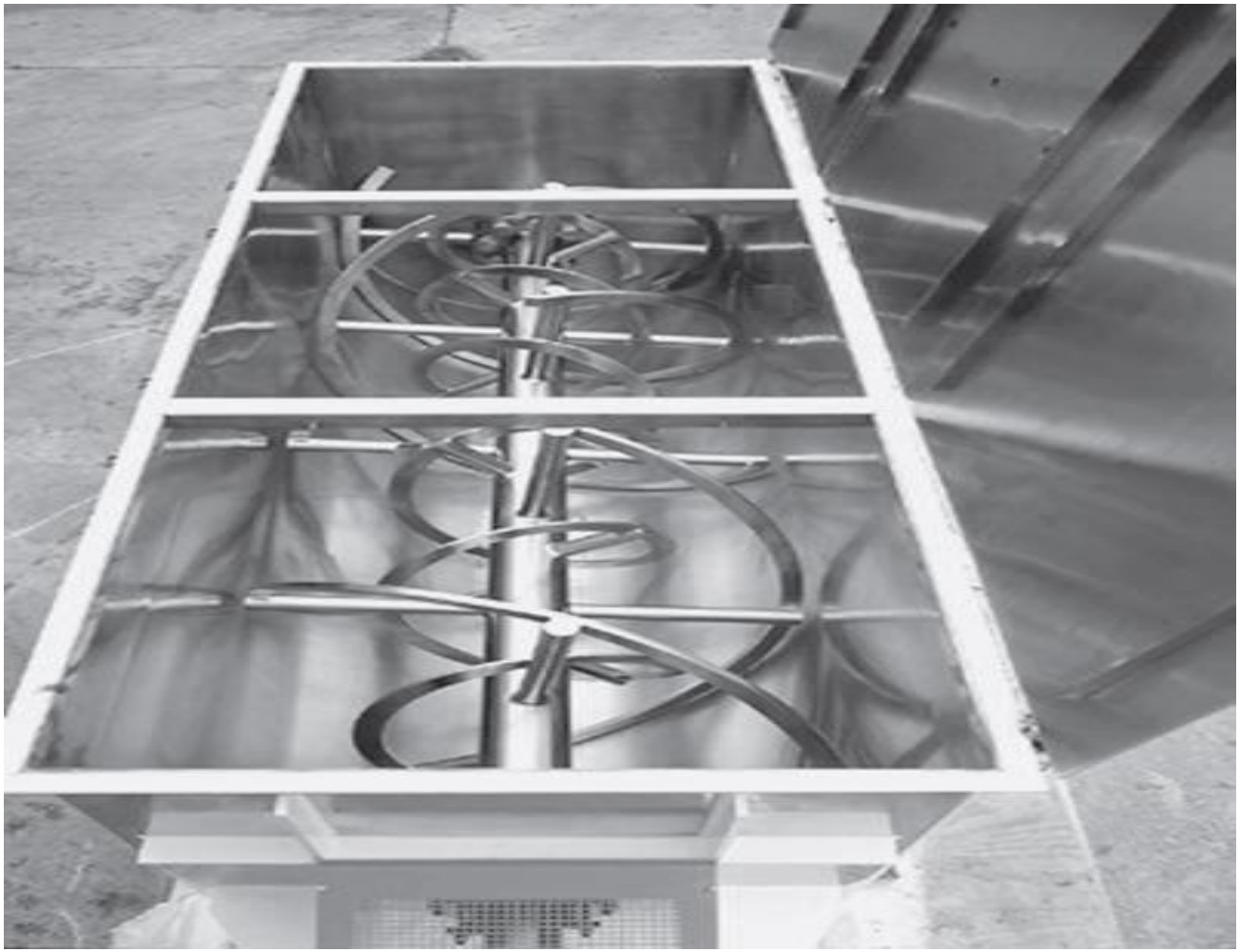

Fig. Ribbon blender

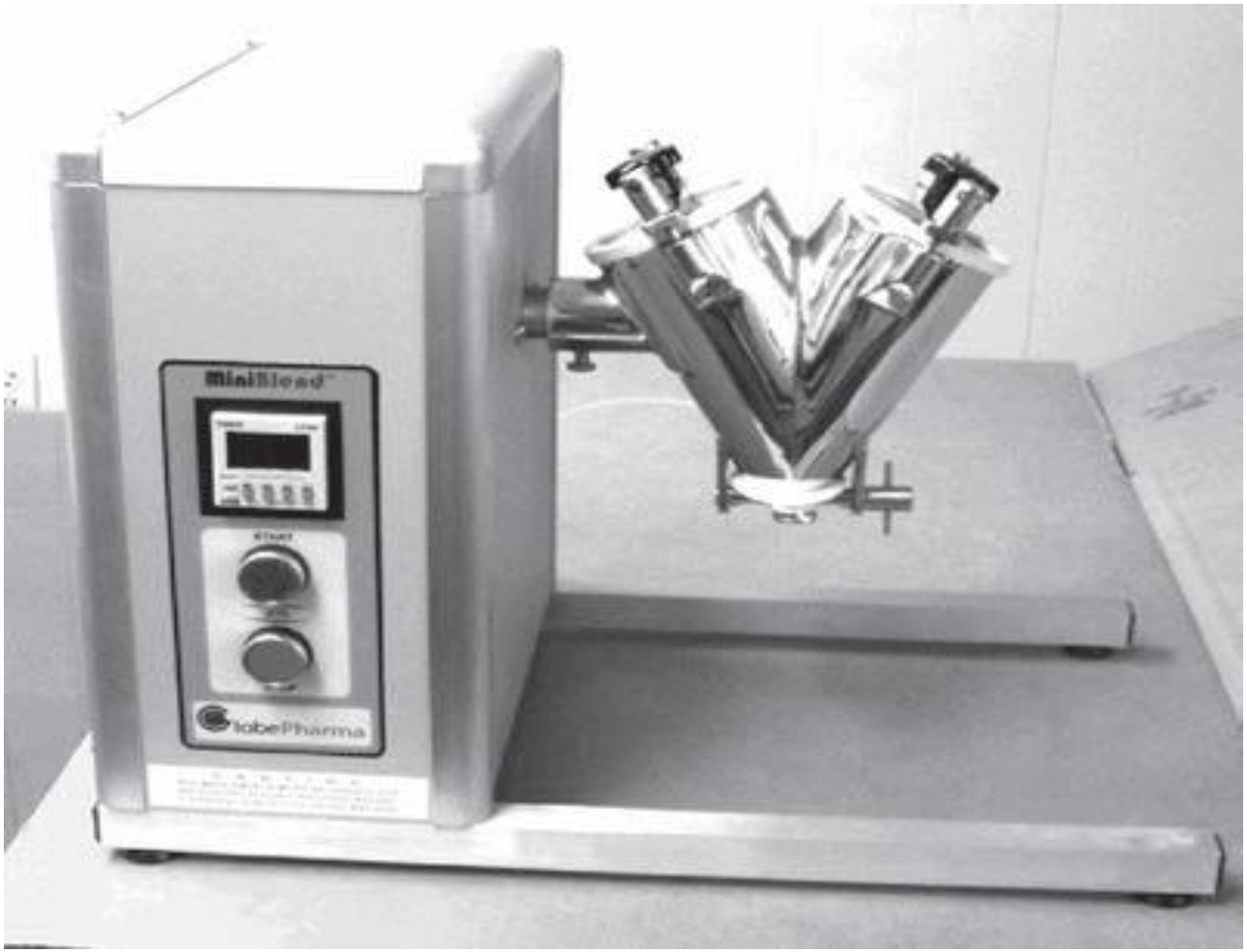

Fig. Laboratory-scale V-blender

Fig. Laboratory-scale Triple V-type blender

- The mixing of powders will be affected by:
  - Particle size
  - Density of each component
  - Amount (proportion) of each component

...

Challenges in powder preparations

1. Eutectic mixtures

- When two or more substances are mixed together they **liquefy** due to the formation of mixture which has a lower melting point than room temperature.

- The degree of liquefaction is governed by their melting points, relative proportions and room temperature.

...

2. Hygroscopic and Deliquescent powders

- Absorb moisture from the atmosphere.
- Not suitable for dispensing in powder because the absorbed moisture may promote the chemical degradation of the drug.
- These substances are usually supplied in granular form in order to expose less SA to the atmosphere.

...

- Commonly prescribed hygroscopic substances
  - Ammonium chloride, ammonium bromide, hyosine hydrobromide, ammonium citrate, pepsin, and phenobarbitone sodium
- Deliquescent substances
  - Benzonatate, nicotinic acid, chloral hydrate, and paramethadione

...

3. Vegetable powders

- Vegetable powder which contain volatile oils should not be subjected to heavy grinding in a mortal.
- When it is necessary to powder them, they must be powdered lightly to prevent the loss of volatile oils.
- In dispensing, they must be double wrapped with a wax paper.

...

4. Explosive mixtures

- When an oxidizing agent and reducing agent are triturated together there are chances of explosion.
- The prescription for such combinations in a powder form are rare and preferably shouldn't be filled.
- If it has to be dispensed, powder each ingredient separately and mix them lightly, or dispense them in separate powder paper with suitable directions.

...

5. Potent drugs

- Small quantities of potent drugs could not be weighed on dispensing balance.
  - The best method is to use geometric trituration method.
  - These are dilutions of potent powdered drugs, prepared by mixing of the drug with a suitable diluent in definite proportion.

...

6. Efflorescent powders

- Crystalline substances liberate water of crystallization wholly or partly due to change in the relative humidity or during trituration causing the powder to become wet or liquefy.

- Overcome by using either corresponding anhydrous salt or an inert substances may be mixed with efflorescent substance before incorporating the other ingredients.

...

Types of Dispensed powders

Simple powder

- Contains only one ingredients either in crystalline or amorphous form.
- When the powder is in the crystalline form, preferably it is reduced to fine powder, weighed and wrapped as individual dose.

...

Compound powder

- Contain two or more than two substances which are mixed together.

Divided Powders

- After a powder has been properly blended it may be divided into individual dosing units.
- Each divided portion of powder may be placed on a small piece of paper.

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- The papers may be
  - **Simple bond paper:** a superior grade of strong white paper made wholly or in part from rag pulp
  - **Vegetable parchment:** a thin, semi opaque paper with limited moisture resistance
  - **Glassine paper:** a glazed, transparent paper with limited moisture resistance
  - **Waxed paper:** a transparent waterproof paper

Bulk Powders

- The bulk powders available in prepackaged amounts
  - Antacids and Laxatives
  - Douche powders for vaginal use
  - Medicated powders for external application to the skin

...

- For internal use supplied in wide-mouthed containers in which a teaspoon can be entered for easy removal of the contents
- For external application supplied in cardboard, glass or plastic containers which are often designed for the specific method of application (perforated lid).
- Dispensing powder medication in bulk quantities is limited to **non-potent** substances.

...

- Appropriate instructions to the patient in dispensing bulk powders include:
  - Appropriate handling
  - Storage
  - Measurement, and
  - Preparation of bulk powder, i.e. be told the type of liquid or vehicle to use to deliver the medication.

...

Dusting powders

- Contain ingredients used for therapeutic, prophylactic or lubricant purposes and are intended for external use.
- Only sterile dusting powders should be applied to open wounds.
- Dusting powders for lubricant purposes or superficial skin conditions need not be sterile but they should be free from pathogenic organisms.

...

Aerosol powders

- Are administered by inhalation with the aid of dry-powder inhalers, which deliver micronized particles of medication in **metered** quantities.
- To accomplish this, the particle size of the micronized medication is prepared in the range of 1-6 μm in diameter.
- Most of these products are used in the treatment of asthma and other bronchial disorders.

...

- In addition to the therapeutic agent, these products contain inert **propellants** and pharmaceutical **diluents**
- These aid the formulation's flow properties and metering uniformity and protect the powder from humidity.
- Powder blowers or insufflators may be used to deliver dry powders to various parts of the body.

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- The difficulties of using this apparatus
  - To obtain a measured quantity of drug to get a uniform dose.
  - Tendency to get blocked when the powders used or the apparatus is wet.

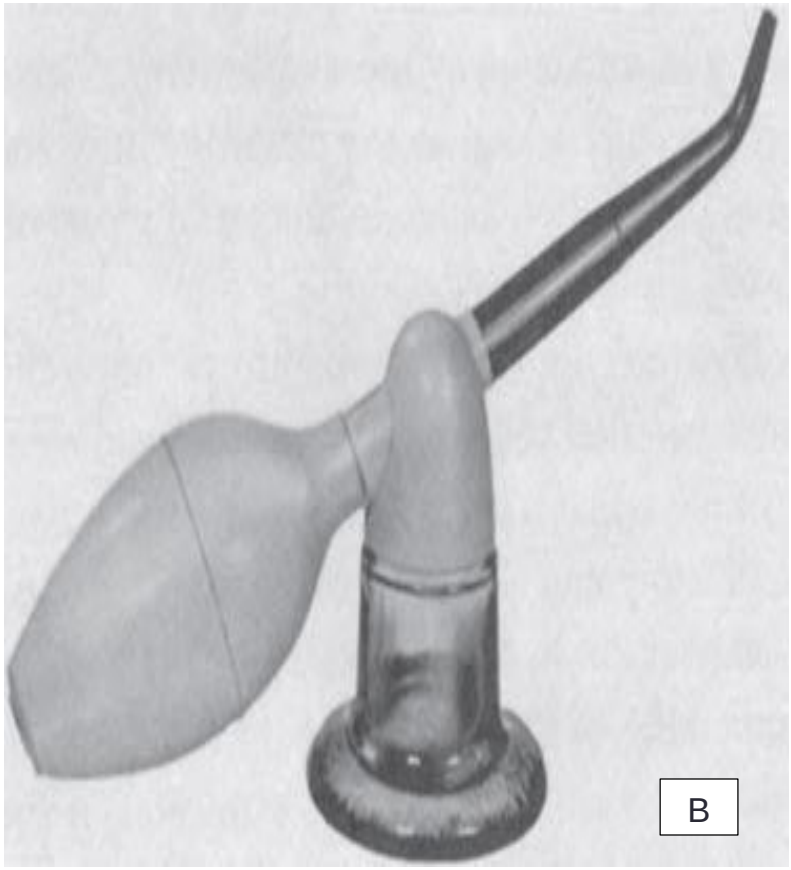

Fig. (A) Metered inhalation aerosol (B) General-purpose powder insufflator

Oral Powders

- Oral powders generally can be supplied as finely divided powders or effervescent granules.
- The finely divided powders are suspended or dissolved in water or mixed with soft foods before administration.
  - Antacids and laxative powders
  - Powdered antibiotics to be reconstituted before administration.

Douche Powders

- Douche powders are completely soluble and are dissolved in water prior to use as antiseptics or cleansing agents for a body cavity.

- They most commonly are intended for vaginal use, although they may be formulated for nasal, otic, or ophthalmic use.

Granules

- Prepared agglomerates of smaller particles of powder.
- Irregularly shaped but may be prepared to be spherical.
- Usually prepared in the 4 to 12-mesh sieve (4.76 to 2.00 mm) size range.
- Used as dosage form or they may be used for pharmaceutical purposes, as in making tablets.

...

- Granules flow well compared to powders.
- Granules have less SA than that of a comparable volume of powder
  - More stable to the effects of atmospheric humidity and are less likely to cake or harden upon standing.
- Granules also are more easily wetted by liquids than are certain light and fluffy powders (which tend to float on the surface).

Granule Preparation

- Two methods
    - Wet method
    - Dry methods

Wet method

- General wet method

Steps

- Moisten the powder or powder mixture
- Pass the resulting paste through a screen of the mesh size to produce the desired size of granules
- Placed on drying trays and are dried by air or under heat
- Periodically moved about on the drying trays to prevent adhesion into a large mass

...

- Fluid bed processing
  - Particles are placed in a conical piece of equipment
  - Vigorously dispersed,
  - Suspended while a liquid excipient is sprayed on the particles and
  - The product dried, forming granules of defined particle size

A

B

Fig. (A) Fluidizing process (B) Fluid bed equipment

...

Dry granulation method

- Roll compactor
  - The dry powder is passed through a roll compactor and then through a granulating machine.
  - Roll compactor processes a fine powder into dense sheets by forcing it through two mechanically rotating metal rolls.
  - The compacted powder is granulated to uniform particle size in a mechanical granulator

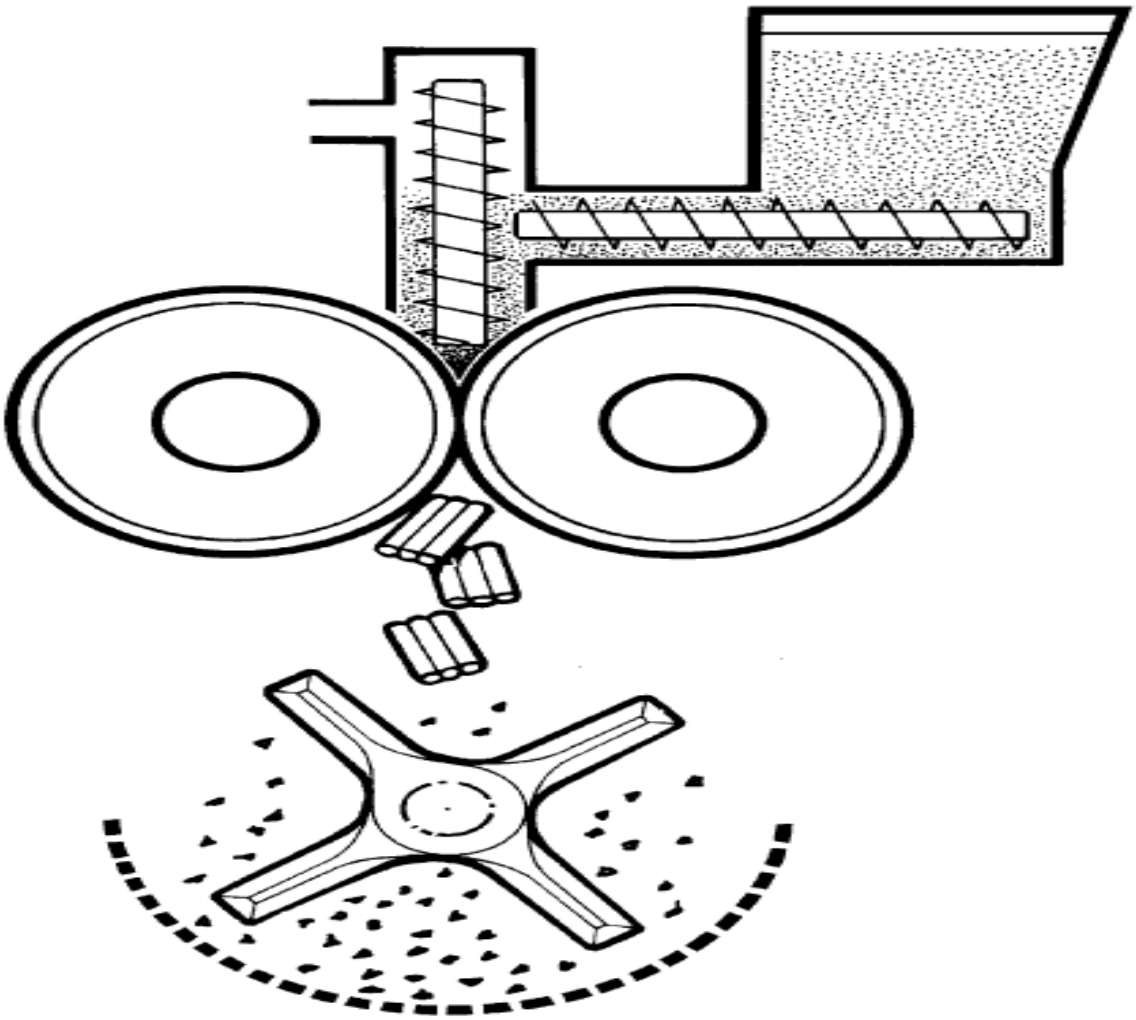

Fig. schematic representation of the roller compaction process.

- Slugging
  - Slugging is the compression of a powder or powder mixture into large slugs on a compressing machine.
  - The slugs are generally flat-faced and are about 2.5 cm in diameter
  - The slugs are granulated into the desired particle size, generally for use in the production of tablets

...

Effervescent Granules

- In addition to active pharmaceutical agent these products composed of base (e.g. sodium bicarbonate) and acids (e.g. citric acid, and tartaric acid).

- On solution in water, carbon dioxide is released because of the acid-base reaction.

  - Citric acid: $3NaHCO_3 + C_6H_8O_7.H2O = C_6H_5Na_3O_7 + 3CO_2 + 3H_2O$

  - Tartaric acid: $2NaHCO_3 + C_4H_6O_6 = C_4H_4Na_2O_6 + 2CO_2 + 2H_2O$

...

- The release of the water of crystallization makes the powder coherent and helps form the granules.
- The effervescence from the release of the carbon dioxide masks the taste of salty or bitter medications.
- Effervescent granules are preferred to effervescent powders in order to prevent violent and uncontrollable effervescence
  - Sudden and rapid effervescence could overflow the glass and leave little residual carbonation in the solution

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- Using a combination of citric and tartaric acids rather than either acid alone avoids certain difficulties
  - When tartaric acid is used as the sole acid, the resulting granules readily lose their firmness and crumble
  - Citric acid alone results in a sticky mixture difficult to granulate
- Should be stored in tightly closed containers and desiccants are usually added to the containers.

...

- Effervescent granules are prepared by two general methods:
    - Dry or fusion method
    - Wet method

- Dry or Fusion Method
  - One molecule of water present in each molecule of citric acid acts as the binding agent for the powder mixture
  - Before mixing the powders, the citric acid crystals are powdered and then mixed with the other powders of the same sieve size to ensure uniformity of the mixture
  - The mixing of the powders is performed as rapidly as is practical, preferably in an environment of low humidity to avoid absorption of moisture and a premature chemical reaction
  - After mixing, the powder is placed on a suitable dish in an oven at 34°C to 40°C

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- The heat releases the water of crystallization from the citric acid, which dissolves a portion of the powder mixture.
  - This causes the softened mass of powder to become somewhat spongy, and
  - When it has reached the proper consistency, it is removed from the oven and rubbed through a sieve to produce granules of the desired size.
  - The granules are dried at a temperature not exceeding 54°C.

- Wet Method
  - The source of binding agent is not the water of crystallization from the citric acid but the water added to alcohol as the moistening agent.
  - Enough liquid is added (in portions) to prepare a mass of proper consistency.
  - The granules are prepared and dried in the same manner as described in dry method.

Advantages of Powders and Granules

- Solid preparations are more stable than liquid preparations.
  - Powders for antibiotic syrups, is 2 to 3 years
  - Reconstituted with water it is 1 to 2 weeks.
- Incompatibility is less in case of powders than liquids.
- They are more easy to carry than liquids.

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- Powders and granules are convenient forms in which to dispense drugs with a large dose.
- Powders & granules of soluble medicaments have a faster dissolution rate than tablets or capsules.
- Powders offer a lot of flexibility in compounding solids.
- More convenient to prescribe specific amount of medicament according to the need of the patient.
- They are more economic.

...

Disadvantages of powders and granules

- Bulk powders or granules are far less convenient for patients to carry than a small container of tablets or capsules.
- The masking of unpleasant tastes may be a problem with this type of preparation.
- Bulk powders or granules are not a good method of administering potent drugs with a low dose.

...

- They are not a suitable method for the administration of drugs that are inactivated in the stomach.
- They are not well suited for dispensing hygroscopic or deliquescent drugs.
- They are not suitable for drugs which deteriorate on exposure to atmospheric conditions.
- Volatile drugs are not suitable for dispensing in powder form.

- Reading assignment
  - Tablets and Capsules